

(Continued)

Analysis of Carcinogenic Potential in Female Mouse
 Test of Dose-Response (Tumor) Positive Linear Trend
 Run Date & Time: March 7, 1997 (14:52)
 Source: c:\amouse\xrod.txt

Dose Levels Included: CTR1 CTR2 LOW MED HIGH MAXI (0 0 25 375 750 1500)

Note: For missing Tumor-Caused-Death set INCIDENTAL
 Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
 Symbols, ^, +, or * represents that the P-value is in
 the range of [0, 0.005), [0.005, 0.025), or [0.025, 0.05)

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TIME TYPE INTERVAL	ROW TABLE	P VALUES		
						EXACT PERMU	ASYMP- TOTIC	CONTINU CORRECT
ADRENAL CO(4401)ADENOMA, TYPE(440118) IN	IN 79-94	1	1.000	0.800	0.800
				IN 79-94	2			
ADRENAL ME(4402)PHEOCHROMOCYT(440201) IN	Tumor rate: 1% in CTL - Total	-	1.000	0.796	0.796
				IN 95-96	1			
SYSTEMIC N(4500)MALIGNANT LYM(450001) MX	IN 95-96	2	0.177	0.177	0.176
				IN 0-52	1			
				IN 0-52	2			
				IN 53-78	1			
				IN 53-78	2			
				IN 79-94	1			
				IN 79-94	2			
				IN 95-96	1			
				IN 95-96	2			
				FA 28	1			
				FA 28	2			
				FA 30	1			
				FA 30	2			
				FA 33	1			
				FA 33	2			
				FA 39	1			
				FA 39	2			
				FA 43	1			
				FA 43	2			
				FA 50	1			
				FA 50	2			
				FA 52	1			
				FA 52	2			
				FA 54	1			
				FA 54	2			
				FA 61	1			
				FA 61	2			
				FA 62	1			
				FA 62	2			
				FA 63	1			
				FA 63	2			
				FA 65	1			
				FA 65	2			
				FA 66	1			
				FA 66	2			
				FA 68	1			
				FA 68	2			
				FA 69	1			
				FA 69	2			
				FA 70	1			
				FA 70	2			
				FA 73	1			

(Continued)

Analysis of Carcinogenic Potential in Female Mouse
 Test of Dose-Response (Tumor) Positive Linear Trend
 Run Date & Time: March 7, 1997 (14:52)
 Source: c:\amcuse\xrod.txt

Dose Levels Included: CTR1 CTR2 LOW MED HIGH MAXI (0 0 25 375 750 1500)

Note: For missing Tumor-Caused-Death set INCIDENTAL

Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
 Symbols, ^, +, or * represents that the P-value is in
 the range of [0, 0.005), [0.005, 0.025), or [0.025, 0.05)

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TIME TYPE INTERVAL	ROW TABLE	P VALUES		
						EXACT PERMU	ASYMP- TOMIC	CONTINU CORRECT
SYSTEMIC N(4500)				IN 53-78	1	0.488	0.467	0.467
				IN 53-78	2			
				IN 79-94	1			
				IN 79-94	2			
				IN 95-96	1			
				IN 95-96	2			
				Tumor rate: 1% in CTL - Total	-			
				(MYELOID LEUKE(450004)) MX IN 95-96	1			
				IN 95-96	2			
				FA 67	1			
				FA 67	2			
				FA 74	1			
				FA 74	2			
				FA 89	1			
				FA 89	2			
SPLEEN	(4600)			Tumor rate: 2% in CTL - Total	-	0.597	0.575	0.575
				(HISTIOCYTIC S(040015)) MX FA 57	1			
				FA 57	2			
				FA 95	1			
SPLEEN	(4600)			FA 95	2	0.371	0.301	0.301
				Tumor rate: 1% in CTL - Total	-			
				(HEMANGIOSARCO(180003)) MX FA 82	1			
				FA 82	2			
THYMUS	(5000)			Tumor rate: <1% in CTL - Total	-	0.556	0.549	0.549
				(HISTIOCYTIC S(040015)) MX IN 53-78	1			
				IN 53-78	2			
				FA 95	1			
THYMUS	(5000)			FA 95	2	0.419	0.535	0.536
				Tumor rate: 1% in CTL - Total	-			
				(THYMOMA (B) (500012)) IN IN 53-78	1			
				IN 53-78	2			
LYMPH NODE(5100)				IN 95-96	1	0.348	0.294	0.294
				IN 95-96	2			
				Tumor rate: <1% in CTL - Total	-			
				(HISTIOCYTIC S(040015)) MX FA 95	1			
LYMPH NODE(5100)				FA 95	2	0.250	0.054	0.054
				Tumor rate: <1% in CTL - Total	-			
				(HEMANGIOMA (C(160212)) IN IN 0-52	1			
				IN 0-52	2			
LYMPH NODE(5100)				Tumor rate: <1% in CTL - Total	-	1.000	0.796	0.796
				(METASTATIC CA(510016)) IN IN 95-96	1			

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(Continued)


Analysis of Carcinogenic Potential in Female Mouse
 Test of Dose-Response (Tumor) Positive Linear Trend
 Run Date & Time: March 7, 1997 (14:52)
 Source: c:\amouse\xrod.txt

Dose Levels Included: CTRL CTR2 LOW MED HIGH MAXI (0 0 25 375 750 1500)

Note: For missing Tumor-Caused-Death set INCIDENTAL

Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)

Symbols, ^, +, or * represents that the P-value is in the range of [0, 0.005), [0.005, 0.025), or [0.025, 0.05)

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TIME TYPE	INTERVAL	ROW	TABLE	P VALUES		
								EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
MESENT. LY(5104))HISTIOCYTIC S(040015)	MX	FA	IN 95-96	2		0.348	0.294	0.294
					- Total	-				
					FA 95	1				
					FA 95	2				
MESENT. LY(5104))HEMANGIOMA (C(160212)	IN	IN	Tumor rate: <1% in CTL - Total	-		0.889	0.874	0.874
					IN 79-94	1				
					IN 79-94	2				
					IN 95-96	1				
HARDERIAN (5400))ADENOCARCINOM(160110)	MX	IN	IN 95-96	2		0.060	0.052	0.052
					- Total	-				
					IN 53-78	1				
					IN 53-78	2				
HARDERIAN (5400))ADENOMA (C) (160112)	IN	IN	IN 79-94	1		0.531	0.598	0.598
					IN 79-94	2				
					IN 95-96	1				
					IN 95-96	2				
MAMMARY GL(5600))ADENOCARCINOM(160110)	MX	IN	Tumor rate: 1% in CTL - Total	-		0.985	0.957	0.957
					IN 53-78	1				
					IN 53-78	2				
					IN 79-94	1				
SKIN/SUBCU(5700))MALIGNANT SCH(010012)	MX	IN	IN 79-94	2		0.191	0.137	0.137
					IN 95-96	1				
					IN 95-96	2				
					FA 82	1				
SKIN/SUBCU(5700))HEMANGIOSARCO(180003)	MX	IN	FA 82	2		1.000	0.800	0.800
					FA 86	1				
					FA 86	2				
					- Total	-				
SKIN/SUBCU(5700))HEMANGIOSARCO(180003)	MX	IN	IN 79-94	1				
					IN 79-94	2				

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Analysis of Carcinogenic Potential in Female Mouse
 Test of Dose-Response (Tumor) Positive Linear Trend
 Run Date & Time: March 7, 1997 (14:52)
 Source: c:\mouse\xrod.txt

Dose Levels Included: CTRL CTRL2 LOW MED HIGH MAXI (0 0 25 375 750 1500)

Note: For missing Tumor-Caused-Death set INCIDENTAL

Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)

Symbols, ^, +, or * represents that the P-value is in the range of [0, 0.005), [0.005, 0.025), or [0.025, 0.05)

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TIME TYPE INTERVAL	ROW TABLE	P VALUES		
						EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
SKIN/SUBCU(5700)SQUAMOUS CELL(570001) MX	Tumor rate: 1% in CTL - Total	-	0.659	0.745	0.745
				IN 95-96	1			
				IN 95-96	2			
				FA 77	1			
SKIN/SUBCU(5700)KERATOACANTHO(570020) IN	Tumor rate: <1% in CTL - Total	-	1.000	0.800	0.800
				IN 79-94	1			
				IN 79-94	2			
				FA 77	2			
EARS (6600)MALIGNANT SCH(010012) MX	Tumor rate: 1% in CTL - Total	-	1.000	0.796	0.796
				IN 95-96	1			
				IN 95-96	2			
				FA 57	1			
BODY CAVIT(6800)HISTIOCYTIC S(040015) MX	Tumor rate: 1% in CTL - Total	-	1.000	0.794	0.794
				FA 57	1			
				FA 57	2			
				IN 95-96	1			
TAIL (7400)MALIGNANT SCH(010012) MX	Tumor rate: 1% in CTL - Total	-	1.000	0.796	0.796
				IN 95-96	1			
				IN 95-96	2			
				IN 95-96	2			
Tumor rate: 1% in CTL - Total				-				

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Analysis of dose-response trend in mouse for hemangioma-hemangiosarcoma combined

Analysis of Carcinogenic Potential in Male Mouse
 Test of Dose-Response (Tumor) Positive Linear Trend
 Ted Guo, PH.D, CDER/FDA

Run Date & Time: March 18, 1997 (16:25)

Source: c:_data\cbmice.txt

Note: Dose Levels Included: CTR1 CTR2 LOW MED HIGH MAX1 (0 0 25 375 750 1500)
 For missing Tumor-Caused-Death set INCIDENTAL
 IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
 Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TIME TYPE	INTERVAL	ROW	TABLE	P VALUES		
								EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
ORGANS WITH HEMANG*		HEMANGIOMA+HEMANGIO-SARCOMA		MX	IN 53-78	1		0.225	0.232	0.232
					IN 53-78	2				
					IN 79-91	1				
					IN 79-91	2				
					IN 92-104	1				
					IN 92-104	2				
					IN 105-105	1				
					IN 105-105	2				
					FA 82	1				
					FA 82	2				
					FA 83	1				
					FA 83	2				
					FA 85	1				
					FA 85	2				
					FA 93	1				
					FA 93	2				
					FA 96	1				
					FA 96	2				
					FA 100	1				
					FA 100	2				
					FA 104	1				
					FA 104	2				
				Tumor rate: 10% in CTL - Total		-				
OTHER ORGAN(OTHER)OTHER TUMOR (OTHER		MX	IN 0-52	1		0.889	0.889	0.889
					IN 0-52	2				
					IN 53-78	1				
					IN 53-78	2				
					IN 79-91	1				
					IN 79-91	2				
					IN 92-104	1				
					IN 92-104	2				
					IN 105-105	1				
					IN 105-105	2				
					FA 41	1				
					FA 41	2				
					FA 52	1				
					FA 52	2				
					FA 55	1				
					FA 55	2				
					FA 62	1				
					FA 62	2				
					FA 65	1				
					FA 65	2				
					FA 66	1				
					FA 66	2				
					FA 70	1				
					FA 70	2				
					FA 71	1				

(Continued)

Analysis of Carcinogenic Potential in Male Mouse
 Test of Dose-Response (Tumor) Positive Linear Trend
 Run Date & Time: March 18, 1997 (16:25)
 Source: c:_data\ckmice.txt

Note: Dose Levels Included: CTR1 CTR2 LOW MED HIGH MAXI (0 0 25 375 750 1500)
 For missing Tumor-Caused-Death set INCIDENTAL
 IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
 Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TIME TYPE INTERVAL	ROW TABLE	P VALUES		
						EXACT PERMU	ASYMP- TOTIC	CONTINU CORRECT
				FA 71	2			
				FA 72	1			
				FA 72	2			
				FA 74	1			
				FA 74	2			
				FA 78	1			
				FA 78	2			
				FA 80	1			
				FA 80	2			
				FA 81	1			
				FA 81	2			
				FA 82	1			
				FA 82	2			
				FA 83	1			
				FA 83	2			
				FA 84	1			
				FA 84	2			
				FA 85	1			
				FA 85	2			
				FA 88	1			
				FA 88	2			
				FA 89	1			
				FA 89	2			
				FA 90	1			
				FA 90	2			
				FA 91	1			
				FA 91	2			
				FA 93	1			
				FA 93	2			
				FA 94	1			
				FA 94	2			
				FA 96	1			
				FA 96	2			
				FA 98	1			
				FA 98	2			
				FA 99	1			
				FA 99	2			
				FA 100	1			
				FA 100	2			
				FA 101	1			
				FA 101	2			
				FA 102	1			
				FA 102	2			
				FA 103	1			
				FA 103	2			
				FA 104	1			
				FA 104	2			

Tumor rate: 87% in CTL - Total

Analysis of Carcinogenic Potential in Female Mouse
 Test of Dose-Response (Tumor) Positive Linear Trend
 Ted Guc, FH.D, CDER/FDA

Run Date & Time: March 18, 1997 (16:29)

Source: c:_data\cbmice.txt

Note: Dose Levels Included: CTR1 CTR2 LOW MED HIGH MAXI (0 0 25 375 750 1500)
 For missing Tumor-Caused-Death set INCIDENTAL
 IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
 Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TIME TYPE INTERVAL	ROW	TABLE	P VALUES		
							EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
ORGANS WITH HEMANG*		HEMANGIOMA+HEMANGIO-SARCOMA		MX IN 0-52	1		0.331	0.336	0.336
				IN 0-52	2				
				IN 79-91	1				
				IN 79-91	2				
				IN 92-104	1				
				IN 92-104	2				
				FA 69	1				
				FA 69	2				
				FA 82	1				
				FA 82	2				
				FA 85	1				
				FA 85	2				
				FA 91	1				
				FA 91	2				
				FA 94	1				
				FA 94	2				
				Tumor rate: 6% in CTL - Total	-				
OTHER ORGANS (OTHER)		OTHER TUMORS (OTHER)		MX IN 0-52	1		0.188	0.189	0.190
				IN 0-52	2				
				IN 53-78	1				
				IN 53-78	2				
				IN 79-91	1				
				IN 79-91	2				
				IN 92-104	1				
				IN 92-104	2				
				FA 28	1				
				FA 28	2				
				FA 30	1				
				FA 30	2				
				FA 33	1				
				FA 33	2				
				FA 39	1				
				FA 39	2				
				FA 43	1				
				FA 43	2				
				FA 50	1				
				FA 50	2				
				FA 52	1				
				FA 52	2				
				FA 54	1				
				FA 54	2				
				FA 57	1				
				FA 57	2				
				FA 61	1				
				FA 61	2				
				FA 62	1				
				FA 62	2				
				FA 63	1				

(Continued)

Analysis of Carcinogenic Potential in Female Mouse
 Test of Dose-Response (Tumor) Positive Linear Trend
 Run Date & Time: March 18, 1997 (16:29)
 Source: c:_data\cbmice.txt

Note: Dose Levels Included: CTR1 CTR2 LOW MED HIGH MAXI (0 0 25 375 750 1500)
 For missing Tumor-Caused-Death set INCIDENTAL
 IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
 Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TIME TYPE INTERVAL	ROW TABLE	P VALUES		
						EXACT PERMU	ASYMP- TOTIC	CONTINU CORRECT
				FA 63	2			
				FA 65	1			
				FA 65	2			
				FA 66	1			
				FA 66	2			
				FA 67	1			
				FA 67	2			
				FA 68	1			
				FA 68	2			
				FA 69	1			
				FA 69	2			
				FA 70	1			
				FA 70	2			
				FA 72	1			
				FA 72	2			
				FA 73	1			
				FA 73	2			
				FA 74	1			
				FA 74	2			
				FA 75	1			
				FA 75	2			
				FA 76	1			
				FA 76	2			
				FA 77	1			
				FA 77	2			
				FA 78	1			
				FA 78	2			
				FA 79	1			
				FA 79	2			
				FA 80	1			
				FA 80	2			
				FA 81	1			
				FA 81	2			
				FA 82	1			
				FA 82	2			
				FA 83	1			
				FA 83	2			
				FA 84	1			
				FA 84	2			
				FA 85	1			
				FA 85	2			
				FA 86	1			
				FA 86	2			
				FA 87	1			
				FA 87	2			
				FA 88	1			
				FA 88	2			
				FA 89	1			
				FA 89	2			

(Continued)

Analysis of Carcinogenic Potential in Female Mouse
 Test of Dose-Response (Tumor) Positive Linear Trend
 Run Date & Time: March 18, 1997 (16:29)
 Source: c:_data\cbmice.txt

Note: Dose Levels Included: CTR1 CTR2 LOW MED HIGH MAXI (0 0 25 375 750 1500)
 For missing Tumor-Caused-Death set INCIDENTAL
 IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
 Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TIME TYPE INTERVAL	ROW TABLE	P VALUES		
						EXACT PERMU	ASYMP- TOTIC	CONTINU CORRECT
				FA 90	1			
				FA 90	2			
				FA 91	1			
				FA 91	2			
				FA 92	1			
				FA 92	2			
				FA 93	1			
				FA 93	2			
				FA 94	1			
				FA 94	2			
				FA 95	1			
				FA 95	2			

Tumor rate: 90% in CTL - Total

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Analysis of dose-response trend in mouse for hemangioma -hemangiosarcoma separately

Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Ted Guo, PH.D, CDER/FDA

Run Date & Time: March 19, 1997 (8:34)

Source: c:_data\hemice.txt

Note: Dose Levels Included: CTRL CTR2 LOW MED HIGH MAXI (0 0 25 375 750 1500)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TIME TYPE	INTERVAL	ROW	TABLE	P VALUES			
								EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT	
ORGAN WITH(ORG/1602)HEMANGIOMA (C(160212) IN							IN 53-78	1	0.420	0.440	0.440
							IN 53-78	2			
							IN 92-104	1			
							IN 92-104	2			
							IN 105-105	1			
							IN 105-105	2			
Tumor rate: 4% in CTL - Total							-				
ORGAN WITH(ORG/1800)HEMANGIOSARCO(180003) MX							IN 79-91	1	0.199	0.199	0.199
							IN 79-91	2			
							IN 92-104	1			
							IN 92-104	2			
							IN 105-105	1			
							IN 105-105	2			
							FA 82	1			
							FA 82	2			
							FA 83	1			
							FA 83	2			
							FA 85	1			
							FA 85	2			
							FA 93	1			
							FA 93	2			
							FA 96	1			
							FA 96	2			
							FA 100	1			
							FA 100	2			
							FA 104	1			
							FA 104	2			
Tumor rate: 6% in CTL - Total							-				
OTHER ORGAN(OTHER)OTHER TUMOR (OTHER) MX							IN 0-52	1	0.889	0.888	0.887
							IN 0-52	2			
							IN 53-78	1			
							IN 53-78	2			
							IN 79-91	1			
							IN 79-91	2			
							IN 92-104	1			
							IN 92-104	2			
							IN 105-105	1			
							IN 105-105	2			
							FA 41	1			
							FA 41	2			
							FA 52	1			
							FA 52	2			
							FA 55	1			
							FA 55	2			
							FA 62	1			
							FA 62	2			
							FA 65	1			

(Continued)

Analysis of Carcinogenic Potential in Male Mouse
 Test of Dose-Response (Tumor) Positive Linear Trend
 Run Date & Time: March 19, 1997 (8:34)
 Source: c:_data\hemice.txt

Note: Dose Levels Included: CTRL CTR2 LOW MED HIGH MAXI (0 0 25 375 750 1500)
 For missing Tumor-Caused-Death set INCIDENTAL
 IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
 Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TIME TYPE INTERVAL	ROW TABLE	P VALUES		
						EXACT PERMU	ASYMP- TOTIC	CONTINU CORRECT
				FA 65	2			
				FA 66	1			
				FA 66	2			
				FA 70	1			
				FA 70	2			
				FA 71	1			
				FA 71	2			
				FA 72	1			
				FA 72	2			
				FA 74	1			
				FA 74	2			
				FA 78	1			
				FA 78	2			
				FA 80	1			
				FA 80	2			
				FA 81	1			
				FA 81	2			
				FA 82	1			
				FA 82	2			
				FA 83	1			
				FA 83	2			
				FA 84	1			
				FA 84	2			
				FA 85	1			
				FA 85	2			
				FA 88	1			
				FA 88	2			
				FA 89	1			
				FA 89	2			
				FA 90	1			
				FA 90	2			
				FA 91	1			
				FA 91	2			
				FA 93	1			
				FA 93	2			
				FA 94	1			
				FA 94	2			
				FA 96	1			
				FA 96	2			
				FA 98	1			
				FA 98	2			
				FA 99	1			
				FA 99	2			
				FA 100	1			
				FA 100	2			
				FA 101	1			
				FA 101	2			
				FA 102	1			
				FA 102	2			

(Continued)

Analysis of Carcinogenic Potential in Male Mouse
 Test of Dose-Response (Tumor) Positive Linear Trend
 Run Date & Time: March 19, 1997 (8:34)
 Source: c:_data\hemice.txt

Note: Dose Levels Included: CTRL CTRL2 LOW MED HIGH MAXI (0 0 25 375 750 1500)
 For missing Tumor-Caused-Death set INCIDENTAL
 IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
 Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TIME TYPE INTERVAL	ROW	TABLE	P VALUES		
							EXACT PERMU	ASYMP- TOTIC	CONTINU CORRECT
				FA 103	1				
				FA 103	2				
				FA 104	1				
				FA 104	2				
				Tumor rate: 87% in CTL - Total	-				

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Analysis of Carcinogenic Potential in Female Mouse
 Test of Dose-Response (Tumor) Positive Linear Trend
 Ted Guo, PH.D, CDER/FDA

Run Date & Time: March 19, 1997 (8:40)

Source: c:_data\hemice.txt

Note: Dose Levels Included: CTR1 CTR2 LOW MED HIGH MAXI (0 0 25 375 750 1500)
 For missing Tumor-Caused-Death set INCIDENTAL
 IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
 Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TIME TYPE INTERVAL	ROW TABLE	P VALUES		
						EXACT PERMU	ASYMP- TOTIC	CONTINU CORRECT
ORGAN WITH(ORG/1602)HEMANGIOMA (C(160212)				IN 0-52	1	0.283	0.278	0.278
				IN 0-52	2			
				IN 79-91	1			
				IN 79-91	2			
				IN 92-104	1			
				IN 92-104	2			
				- Total	-			
				MX IN 79-91	1			
				IN 79-91	2			
				IN 92-104	1			
ORGAN WITH(ORG/1800)HEMANGIOSARCO(180003)				IN 92-104	2	0.481	0.494	0.494
				FA 69	1			
				FA 69	2			
				FA 82	1			
				FA 82	2			
				FA 85	1			
				FA 85	2			
				FA 91	1			
				FA 91	2			
				FA 94	1			
				FA 94	2			
				- Total	-			
				MX IN 0-52	1			
				IN 0-52	2			
OTHER ORGA(OTHER)OTHER TUMOR (OTHER)				IN 53-78	1	0.188	0.189	0.190
				IN 53-78	2			
				IN 79-91	1			
				IN 79-91	2			
				IN 92-104	1			
				IN 92-104	2			
				FA 28	1			
				FA 28	2			
				FA 30	1			
				FA 30	2			
				FA 33	1			
				FA 33	2			
				FA 39	1			
				FA 39	2			
				FA 43	1			
				FA 43	2			
				FA 50	1			
				FA 50	2			
				FA 52	1			
				FA 52	2			
				FA 54	1			
				FA 54	2			
				FA 57	1			

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Analysis of Carcinogenic Potential in Female Mouse
 Test of Dose-Response (Tumor) Positive Linear Trend
 Run Date & Time: March 19, 1997 (8:40)
 Source: c:_data\hemice.txt

Note: Dose Levels Included: CTR1 CTR2 LOW MED HIGH MAXI (0 0 25 375 750 1500)
 For missing Tumor-Caused-Death set INCIDENTAL
 IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
 Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TIME TYPE INTERVAL	ROW TABLE	P VALUES		
						EXACT PERMU	ASYMP- TOTIC	CONTINU CORRECT
				FA 57	2			
				FA 61	1			
				FA 61	2			
				FA 62	1			
				FA 62	2			
				FA 63	1			
				FA 63	2			
				FA 65	1			
				FA 65	2			
				FA 66	1			
				FA 66	2			
				FA 67	1			
				FA 67	2			
				FA 68	1			
				FA 68	2			
				FA 69	1			
				FA 69	2			
				FA 70	1			
				FA 70	2			
				FA 72	1			
				FA 72	2			
				FA 73	1			
				FA 73	2			
				FA 74	1			
				FA 74	2			
				FA 75	1			
				FA 75	2			
				FA 76	1			
				FA 76	2			
				FA 77	1			
				FA 77	2			
				FA 78	1			
				FA 78	2			
				FA 79	1			
				FA 79	2			
				FA 80	1			
				FA 80	2			
				FA 81	1			
				FA 81	2			
				FA 82	1			
				FA 82	2			
				FA 83	1			
				FA 83	2			
				FA 84	1			
				FA 84	2			
				FA 85	1			
				FA 85	2			
				FA 86	1			
				FA 86	2			

(Continued)

Analysis of Carcinogenic Potential in Female Mouse
 Test of Dose-Response (Tumor) Positive Linear Trend
 Run Date & Time: March 19, 1997 (8:40)
 Source: c:\data\hemice.txt

Note: Dose Levels Included: CTR1 CTR2 LOW MED HIGH MAXI (0 0 25 375 750 1500)
 For missing Tumor-Caused-Death set INCIDENTAL
 IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
 Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TIME TYPE INTERVAL	ROW TABLE	P VALUES		
						EXACT PERMU	ASYMP- TOTIC	CONTINU CORRECT
				FA 87	1			
				FA 87	2			
				FA 88	1			
				FA 88	2			
				FA 89	1			
				FA 89	2			
				FA 90	1			
				FA 90	2			
				FA 91	1			
				FA 91	2			
				FA 92	1			
				FA 92	2			
				FA 93	1			
				FA 93	2			
				FA 94	1			
				FA 94	2			
				FA 95	1			
				FA 95	2			
				Tumor rate: 90% in CTL - Total	-			

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References

- 1 Lin et al (1994). "Statistical Review and Evaluation of Animal Tumorigenicity Studies." Statistics in the Pharmaceutical Industry. Marcel Dekker, Inc. pp. 19-57.
- 2 Thomas et al (1976). "Trend and Homogeneity Analyses of Proportions and Life Table Data." Computers and Biomedical Research. pp. 373-81.
- 3 Peto et al (1980). "Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments. In Long-Term and Short-Term Screening Assays for Carcinogens: An Critical Appraisal, International Agency for Research on Cancer, Lyon, France. IARC Monographs Supplement 2. pp. 311-426.
- Haseman, J. K. (1983). "A re-examination of false-positive rates for carcinogenesis studies." Fundamental and Applied Toxicology 3, pp. 334-9.
- Haseman, J. K. (1984). "Issues in carcinogenicity testing: Dose selection." Fundamental and Applied Toxicology, Vol. 5. pp. 66-78.

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Analysis of Carcinogenic Potential in Male Rat
 Test of Dose-Response (Tumor) Positive Linear Trend
 Run Date & Time: February 26, 1997 (16:10)
 Source: c:\arat\xrod.txt

Dose Levels Included: CTRL1 CTRL2 LOW MEDIUM HIGH (0 0 150 500 1000)

Note: For missing Tumor-Caused-Death set INCIDENTAL

Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)

Symbols [^---] [-#--] [---+] [---*] ^ # + *
 Represent $0 < P < 0.005$ $0.005 \leq P < 0.01$ $0.01 \leq P < 0.025$ $0.025 \leq P < 0.05$ $P < 0.005$ $P < 0.01$ $P < 0.025$ $P < 0.05$

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES		
							EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
					IN 105-106	2			
					FA 52	1			
					FA 52	2			
					FA 78	1			
					FA 78	2			
					FA 102	1			
					FA 102	2			
					Tumor rate: 3% in CTL - Total	-			
HEMOLYMPHO	(4500) HISTIOCYTIC S(450003)	FA	FA 65	1	0.390	0.256	0.256
					FA 65	2			
					Tumor rate: 1% in CTL - Total	-			
SPLEEN	(4600) HISTIOCYTIC S(010010)	MX	FA 65	1	0.193	0.037*	0.037*
					FA 65	2			
					Tumor rate: <1% in CTL - Total	-		[---*]	[---*]
SPLEEN	(4600) HEMANGIOSARCO(460014)	IN	IN 105-106	1	1.000	0.791	0.792
					IN 105-106	2			
					Tumor rate: 1% in CTL - Total	-			
SPLEEN	(4600) SARCOMA, NOT (460016)	MX	IN 105-106	1	1.000	0.791	0.792
					IN 105-106	2			
					Tumor rate: 1% in CTL - Total	-			
SPLEEN	(4600) HEMANGIOMA (C(460018)	MX	IN 105-106	1	0.173	0.030*	0.030*
					IN 105-106	2			
					Tumor rate: <1% in CTL - Total	-		[---*]	[---*]
BONE MARRO	(4700) HISTIOCYTIC S(010010)	MX	FA 65	1	0.193	0.037*	0.037*
					FA 65	2			
					Tumor rate: <1% in CTL - Total	-		[---*]	[---*]
LYMPH NODE	(5100) HISTIOCYTIC S(010010)	MX	IN 0-78	1	0.667	0.240	0.241
					IN 0-78	2			
					Tumor rate: <1% in CTL - Total	-			
MESENT. LY	(5104) HISTIOCYTIC S(010010)	MX	IN 0-78	1	0.667	0.240	0.241
					IN 0-78	2			
					Tumor rate: <1% in CTL - Total	-			
MESENT. LY	(5104) HEMANGIOSARCO(460014)	IN	IN 94-104	1	0.906	0.937	0.937
					IN 94-104	2			
					IN 105-106	1			
					IN 105-106	2			
					Tumor rate: 1% in CTL - Total	-			
MESENT. LY	(5104) HEMANGIOMA (C(460018)	MX	IN 94-104	1	0.729	0.727	0.727
					IN 94-104	2			

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Analysis of Carcinogenic Potential in Male Rat
 Test of Dose-Response (Tumor) Positive Linear Trend
 Run Date & Time: February 26, 1997 (16:10)
 Source: c:\arat\xrod.txt

Dose Levels Included: CTRL1 CTRL2 LOW MEDIUM HIGH (0 0 150 500 1000)

Note: For missing Tumor-Caused-Death set INCIDENTAL

Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)

Symbols [^---] [-&--] [---+] [---*] ^ * + *
 Represent $0 < P < 0.005$ $0.005 \leq P < 0.01$ $0.01 \leq P < 0.025$ $0.025 \leq P < 0.05$ $P < 0.005$ $P < 0.01$ $P < 0.025$ $P < 0.05$

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TIME TYPE INTERVAL	ROW TABLE	P VALUES		
						EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
				IN 105-106	1			
				IN 105-106	2			
				FA 97	1			
				FA 97	2			
				Tumor rate: 18% in CTL - Total	-			
MANDIBUL.	(5108))HISTIOCYTIC S(010010)) MX	IN 0-78	1	0.667	0.240	0.241
				IN 0-78	2			
				Tumor rate: <1% in CTL - Total	-			
HARDERIAN	(5400))HISTIOCYTIC S(010010)) MX	IN 0-78	1	0.667	0.240	0.241
				IN 0-78	2			
				Tumor rate: <1% in CTL - Total	-			
HARDERIAN	(5400))ADENOCARCINOM(540011)) IN	IN 105-106	1	0.378	0.296	0.296
				IN 105-106	2			
				Tumor rate: <1% in CTL - Total	-			
EXORBITAL	(5520))HISTIOCYTIC S(010010)) MX	IN 0-78	1	1.000	0.930	0.930
				IN 0-78	2			
				Tumor rate: 1% in CTL - Total	-			
MAMMARY GL	(5600))HISTIOCYTIC S(010010)) MX	IN 0-78	1	0.667	0.240	0.241
				IN 0-78	2			
				Tumor rate: <1% in CTL - Total	-			
SKIN	(5700))HISTIOCYTIC S(010010)) MX	IN 0-78	1	0.667	0.240	0.241
				IN 0-78	2			
				Tumor rate: <1% in CTL - Total	-			
SKIN	(5700))SQUAMOUS CELL(090038)) FA	FA 99	1	0.648	0.721	0.721
				FA 99	2			
				FA 103	1			
				FA 103	2			
				Tumor rate: <1% in CTL - Total	-			
SKIN	(5700))MALIGNANT SCH(340007)) FA	FA 76	1	0.171	0.154	0.154
				FA 76	2			
				FA 102	1			
				FA 102	2			
				Tumor rate: <1% in CTL - Total	-			
SKIN	(5700))ADENOMA (C) (430006)) IN	IN 105-106	1	1.000	0.791	0.792
				IN 105-106	2			
				Tumor rate: 1% in CTL - Total	-			
SKIN	(5700))HEMANGIOSARCO(460014)) IN	IN 105-106	1	0.546	0.658	0.658
				IN 105-106	2			
				Tumor rate: <1% in CTL - Total	-			

(Continued)

Analysis of Carcinogenic Potential in Male Rat
 Test of Dose-Response (Tumor) Positive Linear Trend
 Run Date & Time: February 26, 1997 (16:10)
 Source: c:\arat\xrod.txt

Dose Levels Included: CTRL1 CTRL2 LOW MEDIUM HIGH (0 0 150 500 1000)

Note: For missing Tumor-Caused-Death set INCIDENTAL

Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)

Symbols [^---] [-%--] [--+-] [---*] ^ % + *

Represent 0<P<0.005 0.005<=P<0.01 0.01<=P<0.025 0.025<=P<0.05 P<0.005 P<0.01 P<0.025 P<0.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES		
							EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
SKIN	(5700)SARCOMA, NOT	(460016) MX	FA 90	1	1.000	0.799	0.799
					FA 90	2			
					Tumor rate: 1% in CTL - Total	-			
SKIN	(5700)HEMANGIOMA (C	(460018) MX	IN 105-106	1	0.378	0.296	0.296
					IN 105-106	2			
					Tumor rate: <1% in CTL - Total	-			
SKIN	(5700)FIBROMA	(570010) IN	IN 105-106	1	0.378	0.296	0.296
					IN 105-106	2			
					Tumor rate: <1% in CTL - Total	-			
SKIN	(5700)KERATOACANTHO	(570011) IN	IN 94-104	1	0.232	0.220	0.220
					IN 94-104	2			
					IN 105-106	1			
					IN 105-106	2			
					Tumor rate: 6% in CTL - Total	-			
SKIN	(5700)SQUAMOUS CELL	(570012) IN	IN 79-93	1	0.248	0.189	0.189
					IN 79-93	2			
					IN 105-106	1			
					IN 105-106	2			
					Tumor rate: 1% in CTL - Total	-			
SKIN	(5700)BASAL CELL CA	(570016) MX	IN 105-106	1	0.329	0.290	0.291
					IN 105-106	2			
					FA 64	1			
					FA 64	2			
					FA 77	1			
					FA 77	2			
					FA 90	1			
					FA 90	2			
					Tumor rate: 3% in CTL - Total	-			
SKIN	(5700)LIPOSARCOMA (((570018) FA	FA 53	1	0.194	0.037*	0.038*
					FA 53	2			
					Tumor rate: <1% in CTL - Total	-			
SKIN	(5700)BASAL CELL AD	(570019) IN	IN 105-106	1	0.522	0.439	0.440
					IN 105-106	2			
					Tumor rate: 1% in CTL - Total	-			
SKIN	(5700)FIBROSARCOMA	(570025) MX	IN 105-106	1	0.449	0.480	0.481
					IN 105-106	2			
					FA 61	1			
					FA 61	2			
					Tumor rate: <1% in CTL - Total	-			
SKIN	(5700)ZYMBAL'S GLAN	(570031) IN	IN 79-93	1	0.191	0.034*	0.034*